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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/937,756 09/25/97 RUEGER

D CRP-070FWCN2

EXAMINER

HM12/0106

PATENT ADMINISTRATOR
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ART UNIT	PAPER NUMBER
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1644

DATE MAILED:

19
01/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/937,756

Applicant(s)

Rueger et al

Examiner

Robert C. Hayes

Group Art Unit

1645

☒ Responsive to communication(s) filed on Sep 29, 1999

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 83, 85, 88-92, 95, 97-99, 101, 105, and 106 is/are pending in the application.

Of the above, claim(s) 83, 89, 92, 95, 98, and 101 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 85, 88, 90, 91, 97, 99, 105, and 106 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 83, 85, 88-92, 95, 97-99, 101, 105, and 106 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

1. The amendment filed 09/20/99 has been entered.
2. The rejection of claims 88, 90-91, 97 & 99 under 35 U.S.C. § 112, second paragraph, as being indefinite for the recitation of “N-CAM or L1 isoform” production by “NG108-15 cells *in vitro*”, and being incomplete, is withdrawn due to the amendment of the claims.
3. The rejection of claims 88 & 90-91 under 35 U.S.C. § 112, second paragraph, as being indefinite for the recitation of a “ % identity” is withdrawn.
4. Applicant's arguments filed 09/20/99 have been fully considered but they are not deemed to be persuasive.
5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
6. This application contains claims 83, 89, 92, 95, 98 & 101 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

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7. Claims 95, 97-99 & 101 are again provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 13-23 of copending Application No. 08/937,755, for the reasons made of record.

Claims 85, 88-92 and new claims 105-106 are again provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 08/937,755, for the reasons made of record.

8. Claims 85, 88, 90-91 & new claims 105-106 are again rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record.

No conception nor proper antecedent basis remains apparent for a sequence having “at least 70% / greater than 60%... from the *C-terminal seven-cysteine* domain... residues 38-139” (i.e., versus “*the amino acid sequence defining the conserved six cysteine* [domain] of hOP-1 (e.g., residues 43-139 of SEQ ID NO. 5)”, as disclosed on page 53 of the specification.

Applicants’ arguments regarding the disclosure on pages 33 and 38 of the specification, in which “generic sequences” are contemplated and discussed, is not equivalent to the different conception regarding “% amino acid homolog”. Nor does the disclosure on pages 40 and 53 describe such a *seven cysteine* domain, as previously made of record; thereby, still constituting new matter.

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No conception nor proper antecedent basis is apparent in context of that disclosed within the specification for the new recitation, "a sequence encoded by a nucleic acid capable of hybridizing with a nucleic acid complementary to a nucleic acid encoding the C-terminal seven-cysteine domain of human OP-1, amino acids 38-139 of SEQ ID NO:5" on pages 64-67 of the specification, in contrast to Applicants' assurances on page 4 of the response. In contrast, pages 64-67 merely contemplates the different conception of use of probes for determining "tissue distribution of morphogens"; thereby, constituting new matter.

No conception nor proper antecedent basis remains apparent in context of that disclosed within the specification for the recitation, "complexed with at least one morphogen *pro* domain polypeptide...", in contrast to Applicants' assurances on page 7 of the response. Again, the mere description of "the mature form of the morphogen may be provided in association with its precursor 'pro' domain..." on page 18 of the specification is not equivalent to the broader scope of adding multiple, or different, polypeptide *pro* domains to any polypeptide, as currently claimed; thereby, still constituting new matter.

No conception nor proper antecedent basis in context of that disclosed within the specification remains for "treating", "restoring motor function", or "preserving motor function" in a mammal afflicted with ALS or spinal cord injury, as previously made of record. In contrast to Applicants' assertions on page 7 of the response, a "method for enhancing survival of neural cells at risk of dying" or "maintaining a [nonspecified] neural pathway" as alleged in original claims 10 & 39, or on pages 8 and 54-63 of the specification, is not equivalent to that now claimed, because

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motor neurons are but a small subclass of neural tissue, in which Applicants failed to conceptualize any “treatment of *motor* neurons” or “restoration of *motor function*” in the original specification; thereby, still constituting new matter.

Thus, Applicants’ arguments are not persuasive for the reasons made of record.

9. Claims 85, 88, 90-91, 97, 99 & new claims 105-106 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to a method of using OP-1 of SEQ ID NO: 4 or 5 to induce N-CAM and L1 expression in NG-108 cells, does not reasonably provide enablement for “treating/preserving motor function/restoring motor function” in a mammal afflicted with ALS/spinal cord injury, or for using structurally uncharacterized morphogens or biologically functional equivalents thereof to accomplish such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons made of record.

Applicants’ argue on pages 8-14 of the response that a) “the Examiner misreads the specification regarding the working examples provided in the specification”, b) “the Examiner misreads the specification regarding the state of the art at the time of filing the specification”, and that c) “the Examiner misreads the state of the art”. However, merely stating that the Examiner’s allegations are “incorrect” by misinterpreting the Examiner’s arguments, or by misquoting

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passages from the specification or from the state of the art references Applicants themselves had initially submitted to support their position, does not justify these above assertions. The issue is not whether Applicants' allegations that "two interpretations in a specification are possible", while citing *In re Wright*, *In re Marzocchi* and *In re Soni*, but that the specification cannot be redefined and then re-interpreted after-the fact, in order to enabled their invention. The record is clear.

1) Page 82 of the specification, in which a 12 mm gap is traversed in a rat sciatic nerve graft experiment using a silicone tube filled with OP-1 gel, specifically demonstrates that graft sites containing *no* OP-1 also showed axonal growth of 12 mm (i.e., axonal growth for 12 mm is not dependent on OP-1); thereby, not requiring OP-1 for sciatic nerve growth, by definition, which is further not commensurate in scope with the unpredictability of the art in "restoring motor function".

2) Page 3 of the specification still accurately summarizes the state of the art in which "[c]urrently, no satisfactory method exists to repair the damage caused by these neuropathies, which include multiple sclerosis,... ALS"....

Accordingly, the state of the art remains unpredictable at the time of filing the instant application, in contrast to Applicants' assertions, as follows:

1) Lein et al. (ref.# C18; Abstract, pg. 597) specifically state "OP-1 requires NGF as a co-factor...in optimal concentrations", and lines 23-25 in the 2nd column of Lein (pg. 597) then teach that "[I]ndeed, the only trophic factor that has been clearly implicated in the regulation of the initial stages of dendritic growth is nerve growth factor (NGF)." In other words, without

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NGF there is no neurite outgrowth/synaptic contact; without OP-1 there is still outgrowth in culture. OP-1 *alone* is, therefore, inert, regardless of the title of the article.

2) Varley et al. specifically state that “OP-1 [i.e., the preferred morphogen of the instant invention] *does not act on a postmitotic cell population*”[emphasis added] (see pgs. 441-442). Therefore, because neurons, including motoneurons, by definition, are postmitotic/amitotic after birth, this reference clearly establishes that the instant invention would not reasonably work *in vivo* in a mammal without undue experimentation to determine otherwise; thereby, not being enabled.

3) Wilson et al. (ref.# C33) specifically disclose that BMPs, in general and as claimed, do not predictably enhance synaptic contacts, in that BMP-4 is conversely a “neural inhibitor” (e.g., pg. 331, Abstract).

4) Withers et al. (ref.# C34) specifically state that “no synaptic contacts were observed”, which is the result of “two possibilities: 1) the OP-1 [i.e., the preferred embodiment of the instant invention] induced dendrites were not receptive to innervation; or 2) the poor growth of axons in these cultures prevented normal synaptic contacts from occurring”. In other words, *in vitro* culturing of sympathetic neurons (i.e., in 1996 vs. the 1992 claimed priority date of the instant invention) still provides no nexus for how to administer a putative protein that may or may not affect motor neurons *in vivo*; nor how to assess when, where or if the invention works *in vivo*; especially when the specification provides no guidance to extrapolate to such treatment. Again, Withers et al. appear to establish that the claimed invention does not work *in vitro*, as claimed,

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and by analogy does not reasonably work *in vivo*, without undue experimentation to determine otherwise. Note hippocampal cultured neurons are not motor neurons, which further were not the subject matter of this article, and in which “synaptic contacts” are not equivalent to the lesser standard of “dendritic development”.

5) Jackowski (IDS ref.# C14) specifically teaches that CNS neurons do not regenerate (pg 305, last *pp*). In other words, because the minimal requirement for restoring motor neuron function is that *de novo* axonal cell growth be completed for a sufficient distance to re-establish a proximity relationship to the prior target, no reasonable expectation of success is expected in the art, without requiring undue experimentation to determine otherwise. Again, neural tissue insults/neuropathy, by definition, lose synaptic contacts and degenerate due to normal Wallerian degeneration (e.g., see Jackowski, pg. 304); and regeneration/restoration of synaptic contacts does not occur either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, pgs. 309-310). In addition, nothing with motor neurons “had already been shown” in Jackowski, in contrast to Applicants’ assertions.

Lastly, consistent with the teachings of Rudinger, because NG108 cells provide no nexus for the skilled artisan to know how to make functional morphogens of the instant invention for use in the claimed methods of the instant invention (i.e., as it relates to 60% or 70% identity, or as it relates to the structurally undefined/uncharacterized morphogens of claims 97, 99 & 105-106),

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and because no assays for determining restoration of “motor function” are disclosed, Applicants’ arguments are not persuasive for the reasons made of record. Furthermore, no documentary evidence supporting Applicant’s assertions that the state of the art at the time of filing enables Applicant’s invention has been made of record (i.e., as it relates to enabling the structural deficient components required for the claimed methods). Nor has any evidence been provided that teaches away from that taught by Rudinger as previously made of record. In particular, nothing described in Dayoff contradicts or supersedes the teachings of Rudinger. In summary, the age of a reference is immaterial to what it teaches; absent new evidence. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977). Therefore, Applicants’ arguments are also not persuasive concerning the unpredictability of the art established by Rudinger for the broadly claimed morphogens required to practice the instant invention, for the reasons made of record.

Thus, for these reasons and because no nexus clearly exists to reasonably extrapolate to Applicants’ claimed invention based on this unpredictability of the art and the limited guidance provided by the instant specification, Applicants’ arguments are not persuasive, for the reasons extensively made of record. It is again noted that enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claims, which Applicants have clearly failed to demonstrate. *In re Hogan and Banks*, 194 USPQ 527 (1977).

10. Claim 85 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing

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to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 85 is dependent on cancelled claim 84.

11. Claims 94, 96-97, 99-100 & 102-104 are again rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because CDMP2 on page 23 appears to indicate that CDMP2 is equivalent to BMP2A and/or BMP2B; thereby, reciting duplicative members of the Markush group.

Applicants' arguments that "BMP2A and BMP2B have different polypeptide sequences (*see*, lines 12-17, the two proteins have different lengths, different pro domains, are different mature proteins)" does not reasonably nor inherently flow from that disclosed on page 23 of the specification; especially when it is stated that it is "referred to in the literature as BMP2A and BMP2B, or BMP2 and BMP4...", versus being separate and distinct proteins.

12. Claims 85, 88, 90-91 & new claims 105-106 are again rejected under 35 U.S.C. 102(b) as being anticipated by The Regents of the University of California/Harland et al. (WO 95/06656; #B5), for the reasons made of record.

As previously made of record, the priority date of the instant application is held to be 09/09/97, because the disclosure within the parent applications were clearly not sufficiently enabled to comply with the requirements of the first paragraph of 35 U.S.C. 112, as extensively prosecuted in these parent applications, for treating any neurodegenerative disease state, or for

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use of the novel dor3 morphogen. It is further noted that it is Applicants' choice to broadly claim that later discovered by others, in which the instant specification had provided no written description of dor3 at the time of filing this application. Further, enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claims. *In re Hogan and Banks*, 194 USPQ 527 (1977). Therefore, Applicants' arguments are not persuasive, because there is nothing "logically inconsistent" or "unfair" with the rejection made of record.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read 'RCH' with a checkmark-like flourish at the end.

Robert C. Hayes, Ph.D.
December 2, 1999

A handwritten signature in black ink, appearing to read 'AC' with a stylized flourish.

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600